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L6: Entry 26 of 47 File: USPT Sep 14, 1999

DOCUMENT-IDENTIFIER: US 5952356 A
TITLE: Pharmaceutical composition

BSPR:
The pharmacologically acceptable salt of the compound represented by the formula (I) or (II) are exemplified by salts with inorganic bases, salts with organic bases, salts with inorganic acids, salts with organic acids, and salts with basic or acidic amino acids.

BSPR:
Preferable examples of salts with inorganic acids include salts with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, etc.

BSPR:
Preferable examples of salts with organic acids include salts with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.

BSPR:
Preferable examples of salts with basic amino acids include salts with arginine, lysine, ornithine, etc., and preferable examples of salts with acidic amino acids include salts with aspartic acid, glutamic acid, etc.

BSPR:
The pharmacologically acceptable salt of the compound represented by the formula (III) is preferably a salt with an inorganic acid, more preferably a salt with hydrochloric acid. Especially, pioglitazone is preferably used in the form of salt with hydrochloric acid.

BSPR:
In the present invention, examples of the drug which is used in combination with the above-mentioned insulin sensitivity enhancer include an .alpha.-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor.

BSPR:
Aldose reductase inhibitors are drugs which inhibit the first-stage rate-limitting enzyme in the polyol pathway to prevent or arrest diabetic complications. In the hyperglycemic state of diabetes, the utilization of glucose in the polyol pathway is increased and the excess sorbitol accumulated intracellularly as a consequence acts as a tissue toxin and hence evokes the onset of complications such as diabetic neuropathy, retinopathy, and nephropathy. Examples of the aldose reductase inhibitors include

BSPR:
Biguanides are drugs having actions of stimulation of anaerobic glycolysis, increase of the sensitivity to insulin in the peripheral tissues, inhibition of glucose absorption from the intestine, suppression of hepatic gluconeogenesis, and inhibition of fatty acid oxidation. Examples of the biguanides include phenformin, metformin, buformin etc.

BSPR:
Squalene synthesis inhibitors are drugs having actions of lowering blood cholesterol levels by inhibiting synthesis of squalene. Examples of the squalene synthesis inhibitors include (S)-.alpha.-[Bis[2,2-dimethyl-1-oxopropoxy)methoxy]phosphinyl]-3-phenoxybenzenebutanesulfonic acid, mono potassium salt (BMS-188494).

BSPR:
Examples of the fibrate compounds include bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, fenofibrate, gemfibrozil, nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate, etc.

BSPR:
Examples of the LDL catabolism enhancers include the compound which is described in JPA H7(1995)-316144 and represented by the formula: ##STR7## wherein R.sup.4, R.sup.5, R.sup.6 and R.sup.7 are the same or different, and represent hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxy group; r is 0-2; s is 2-4; p is 1-2; or a salt thereof; specifically N-[2-[4-bis(4-fluorophenyl)methyl-1-piperazinyl]ethyl]-7,7-diphenyl-2,4,6-heptatrienic acid amide, etc.

BSPR:
The above-mentioned statin compounds, squalene synthesis inhibitors, fibrate compounds and LDL catabolism enhancers can be substituted with other drugs having the property to lower blood cholesterol and triglyceride levels. Examples of these drugs include nicotinic acid derivatives such as nicomol and niceritrol; antioxidants such as probucol; and ion-exchange resins such as colestyramin.

BSPR:
The pharmaceutical composition comprising an insulin sensitivity enhancer in combination with at least one member selected from the group consisting of an .alpha.-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor; and the pharmaceutical composition comprising the compound represented by the formula (II) or a pharmacologically acceptable salt thereof in combination with an insulin secretion enhancer and/or an insulin preparation, both provided in accordance with the present invention, can be respectively put to use by mixing the respective active components either all together or independently with a physiologically acceptable carrier, excipient, binder, diluent, etc. and administering the mixture or mixtures either orally or non-orally as a pharmaceutical composition. When the active components are formulated independently, the respective formulations can be extemporaneously admixed using a diluent or the like and administered or can be administered independently of each other, either concurrently or at staggered times to the same subject.

BSPR:
To manufacture an oral dosage form, an excipient (e.g. lactose, sucrose, starch, mannitol, etc.), a disintegrator (e.g. calcium carbonate, carboxymethylcellulose calcium, etc.), a binder (e.g. .alpha.-starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.), and a lubricant (e.g. talc, magnesium stearate, polyethylene glycol 6000, etc.), for instance, are added to the active component or components and the resulting composition is compressed. Where necessary, the compressed product is coated, by the per se known technique, for masking the taste or for enteric dissolution or sustained release. The coating material that can be used includes, for instance, ethylcellulose, hydroxymethylcellulose, polyoxyethylene glycol, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, and Eudragit (Rohm & Haas, Germany, methacrylic-acrylic copolymer).

BSPR:
A dosage form for external application can be manufactured by processing the active component or components into a solid, semi-solid or liquid composition. To manufacture a solid composition, for instance, the active component or components, either as they are or in admixture with an excipient (e.g. lactose, mannitol, starch, microcrystalline cellulose, sucrose, etc.), a thickener (e.g. natural gums, cellulose derivatives, acrylic polymers, etc.), etc., are processed into powders. The liquid composition can be manufactured in substantially the same manner as the injections mentioned above. The semi-solid composition is preferably provided in a hydrous or oily gel form or an ointment form. These compositions may optionally contain a pH control agent (e.g. carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), among other additives.

BSPR:
Suppositories can be manufactured by processing the active component or components into an oily or aqueous composition, whether solid, semi-solid or liquid. The oleaginous base that can be used includes, for instance, higher fatty acid glycerides [e.g. cacao butter, Witepsols (Dinamit-Nobel), etc.], medium-chain fatty acids [e.g. Migriols (Dinamit-Nobel), etc.], vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil, etc.), etc. The water-soluble base includes, for instance, polyethylene glycols, propylene glycol, etc. The hydrophilic base includes, for instance, natural gums, cellulose derivatives, vinyl polymers, and acrylic polymers, etc.

BSPU:
tolurestat; epalrestat;
3,4-dihydro-2,8-diisopropyl-3-thioxo-2H-1,4-benzoxazine-4-acetic acid;
2,7-difluorospiro(9H-fluorene-9,4'-imidazolidine)-2',5'-dione (generic name: imirestat);

BSPU:
3-[(4-bromo-2-fluorophenyl)methyl]-7-chloro-3,4-dihydro-2,4-dio xo-1(2H)-qui nazoline acetic acid (generic name: zenarestat);

BSPV:
1) Pharmaceutical composition which comprises an insulin sensitivity enhancer in combination with at least one member of the group consisting of an .alpha.-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a LDL catabolism enhancer and an angiotensin converting enzyme inhibitor;

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